

AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111

Serial Number: 09/702068

Filing Date: October 30, 2000

Title: Enzymatic Treatment of Whey Proteins for the Production of Antihypertensive Peptides and the Resulting Products

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REMARKS

Claims 5-6, 13, 15, and 32 are amended, and claims 33-39 are added. As a result, claims 1-3 and 5-39 are now pending in this application. Claim 6 has been withdrawn from Examination.

The amendment to claims 5-6, 13, 15, and 32, and new claims 33-39 are supported by the application as filed, and no new matter has been added.

I. The Interview Summary

Applicant would like to thank Examiner Meller for the courtesy extended during the in-person interview on August 07, 2003. Inventor Dr. Anand Rao and Applicant's attorneys Robert Harris and Peter Malen attended the interview.

The pending claims and cited art were discussed during the interview. Applicant agreed to summarize the meeting in this response and to provide additional claims for consideration.

Dr. Rao and Applicant's attorneys pointed out that claim 1 recites a process for preparing an ACE-inhibiting composition that involves the drying of a hydrolysate, and that none of the cited documents involve such a step. Dr. Rao and Applicant's attorneys also pointed out that claim 1 recites the use of a starting material (a whey protein fraction) and the use of trypsin; and that none of the cited documents disclose a process that involves these two elements.

Applicant would also like to direct the Examiner's attention to independent claims 12 and 13, which recite processes for preparing an ACE-inhibiting composition. These independent claims include additional details related to the starting material (claims 12 and 13) and to the molecular weight profile of the hydrolysate (claim 13). Similarly, dependent claims 8, 10, 16-25, 29, and 35-39 include additional details related to the starting material, and dependent claims 7, 9, 11, 14, 15, and 30-31 include additional details related to the hydrolysate.

The above account is believed to be a complete and accurate summary of the interview as required by 37 C.F.R. § 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicant respectfully requests that the Examiner point out any deficiencies in his next communication so that Applicant can amend or supplement the interview summary.

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II. The Restriction Requirement

The Examiner required restriction to one of the following groups: Group I, directed to processes for an preparing angiotensin-converting enzyme (ACE)-inhibiting composition, and hydrolysates prepared by such processes (claims 1-3, 5, and 7-32); and Group II, directed to a treatment regimen for a mammal to inhibit ACE (claim 6). On February 04, 2003, attorney Peter Malen left a voicemail message for Examiner Meller provisionally electing, with traverse, the claims of Group I. Applicant affirms the election of the claims of Group I, with traverse.

Applicant respectfully traverses the Restriction Requirement. The Restriction Requirement is traversed on the basis that Restriction Requirements are optional in all cases. M.P.E.P. § 803. If the search and examination of an entire application can made without serious burden, the Examiner must examine it on the merits, even though it arguably may include claims to distinct or independent inventions. M.P.E.P. § 803. In light of this, it is submitted that Applicant should not be required to incur additional costs associated with the filing of multiple divisional applications in order to obtain protection for the claimed subject matter. Thus, reconsideration and withdrawal of the Restriction Requirement is respectfully requested.

III. Rejoinder of Claim 6 under M.P.E.P. § 821.04

Claim 6 has been withdrawn from consideration by the Examiner. If product claim 5 or 32 is found to be allowable, rejoinder of claim 6, which recites the administration of the product of claim 5 or 32, is hereby requested.

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IV. Related Co-pending Applications

Applicant would like to bring to the Examiner's attention the following related co-pending applications in the above-identified patent application.

Serial No.	Filing Date	Attorney Docket	Title
09/567,283	May 08, 2000	267.014US1	TREATMENT OF HYPERTENSION IN MAMMALS WITH HYDROLYZED WHEY PROTEINS
10/291,860	Nov. 08, 2002	267.014US2	ENZYMATIC TREATMENT OF WHEY PROTEINS FOR THE PRODUCTION OF ANTIHYPERTENSIVE PEPTIDES, THE RESULTING PRODUCTS AND TREATMENT OF HYPERTENSION IN MAMMALS

V. The 35 U.S.C. § 102(b) Rejections of the Claims

The Examiner rejected claims 1, 2, 5, 7-9, 16-27 and 32 under 35 U.S.C. § 102(b), alleging that those claims are anticipated by JP 04282400 or JP 4282398. The Examiner also rejected claims 5 and 32 under 35 USC § 102(b), alleging that those claims are anticipated by JP 04082898. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Independent claim 1 recites a process for preparing an angiotensin-converting enzyme (ACE)-inhibiting composition comprising: preparing an aqueous solution of a whey protein fraction and a proteolytic enzyme, wherein the proteolytic enzyme is trypsin; holding said solution under conditions effective for reaction to partially hydrolyze said whey protein fraction to provide a hydrolysate having increased ACE-inhibiting activity; stopping the reaction; and drying said hydrolysate. Claims 2, 7-9, 16-24, and 26-27 depend either directly or indirectly from claim 1. Claim 25 depends from claims 12 or 13, neither of which were rejected under 35 U.S.C. § 102(b).

Claim 5 recites an ACE-inhibiting composition as prepared according to claim 1. Claim 32 recites an ACE-inhibiting composition as prepared according to claim 12 or 13. Claims 12 and 13 are independent claims directed to processes for preparing ACE-inhibiting compositions.

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Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon*, 919 F.2d 688, 16 U.S.P.Q.2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

JP 04282400 (hereinafter '400)

The Examiner rejected claims 1, 2, 5, 7-9, 16-27 and 32 under 35 U.S.C. § 102(b), alleging that those claims are anticipated by '400.

'400 describes a process for producing a peptide described as being an inhibitor of ACE (see the final line of page 1). The '400 process begins by dissolving 100 grams of cheese whey powder into 1 liter of distilled water. That solution is subjected to dialysis. Following a pH adjustment, 100 milligrams of bovine trypsin is added. Following 12 hours of hydrolysis, unhydrolyzed proteins and trypsin are precipitated, and the solution is subject to centrifugation. The resulting supernatant is then subjected to ultrafiltration. The peptide is then separated from the solution with a reverse resin column. Following desorption of the peptide, a final product of 100 milligrams of a purified peptide is freeze-dried. The resulting peptide is reported to have an ACE-inhibiting activity of 40 µg/ml.

Claim 1 recites "drying said hydrolysate". In contrast, '400 does not include the step of drying the hydrolysate. Rather, following hydrolysis, the process of '400 involves multiple steps to purify the hydrolysate to provide a peptide, which is then freeze-dried. The hydrolysate prepared in '400 is not dried. Therefore, the process discussed in '400 does not include all of the elements recited in claim 1. Thus, '400 does not anticipate independent claim 1. Because claims 2, 7-9, 16-24, and 26-27 depend either directly or indirectly from claim 1, '400 does not anticipate those claims as they depend from claim 1.

Claim 5 recites an ACE-inhibiting composition as prepared according to claim 1. Claim 32 recites an ACE-inhibiting composition as prepared according to claim 12 or 13. While the product of '400 is a dried, purified peptide, the products prepared according to claims 1, 12, and

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13 are dried hydrolysates. In contrast to the peptide product of '400, the hydrolysates of claims 1, 12 and 13 have not been subjected to the multiple purification procedures of '400. Therefore, it is not reasonable to conclude that the hydrolysates prepared using the processes of the instant claims would be identical to the purified peptide of '400. Thus, '400 does not anticipate claims 5 or 32.

JP 4282398 (hereinafter '398)

The Examiner rejected claims 1, 2, 5, 7-9, 16-27 and 32 under 35 U.S.C. § 102(b), alleging that those claims are anticipated by '398. '398 describes a process for producing a peptide, described as being an inhibitor of angiotensin converting enzyme (ACE), that contains the amino acid sequence Phe-Asp-Lys. *doings*

Similarly to '400, '398 does not include the step of drying a hydrolysate. Therefore, '398 does not anticipate independent claim 1. Because claims 2, 3, 7-11, and 16-24, and 26-31 depend either directly or indirectly from claims 1, '398 does not anticipate those claims as they depend from claim 1.

Again, similarly to '400, the product of '398 is a purified peptide. Therefore, it is not reasonable to conclude that the hydrolysates prepared using the processes of the instant claims would be identical to the purified peptide of '398. Thus, '398 does not anticipate claims 5 or 32.

JP 04082898 (hereinafter '898)

'898 describes a process for producing the specific peptide Leu-Lys-Pro from whey protein by hydrolysis with an aspartic proteinase, followed by extensive purification. This peptide is described as being an inhibitor of ACE. *doings*

As the Examiner acknowledged at page 5 of the pending Office Action, in contrast to claims 1, 12, and 13, '898 does not teach the use trypsin in the hydrolysis reaction. It is well known that the use of different enzymes in hydrolysis reactions will yield different compositions following hydrolysis (see, for example, page 2, lines 25-27 of the specification). Therefore, Applicant respectfully submits that it is not reasonable to conclude that hydrolysates prepared using trypsin (claims 5 and 32) would be identical to a hydrolysate prepared using an aspartic proteinase, as reported in '898. Thus, the product prepared in '898 would have a different

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composition from the claimed products prepared using trypsin. Thus, '898 does not anticipate independent claims 5 or 32.

Conclusion

Applicant submits that none of the cited documents anticipate the claims because no single document discloses every element of a claim under consideration. Accordingly, the Examiner is respectfully requested to withdraw the rejections of the claims under 35 U.S.C. § 102(b).

VI. The 35 U.S.C. § 103 Rejections of the Claims

The Examiner rejected claims 1-3, 5, and 7-32 under 35 U.S.C. § 103(a), alleging that those claims are unpatentable over JP 4282398 or JP 04282400 taken with JP 04082898 and further taken with Ju et al. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Claim 1 is discussed hereinabove.

Claim 12 recites a process for preparing an angiotensin-converting enzyme (ACE)-inhibiting composition comprising: preparing an aqueous solution of a whey protein fraction produced by ion exchange and a proteolytic enzyme, wherein the proteolytic enzyme is trypsin; holding said solution under conditions effective for reaction to partially hydrolyze said whey protein fraction to provide a hydrolysate having increased ACE-inhibiting activity; stopping the reaction when a degree of hydrolysis is reached within the range of from 5.5 to 6.5%, wherein said hydrolysate is characterized by the following Molecular Weight Profile (HPLC)

Range (Daltons)	Soluble Peptides
> 5000	50 - 55%
2000 - 5000	15 - 20%
< 2000	30 - 35%; and

drying said hydrolysate. Claims 16-28 depend either directly or indirectly from claim 12.

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Claim 13 recites a process for preparing an angiotensin-converting enzyme (ACE)-inhibiting composition comprising: a) preparing an aqueous solution of a whey protein fraction, prepared by ion exchange processing and characterized by a protein content of at least 94% and an ash content of less than 3%, and trypsin; b) holding said aqueous solution under conditions effective for reaction to partially hydrolyze said whey protein fraction to provide a hydrolysate; c) stopping said reaction to provide a hydrolysate solution; and d) drying said hydrolysate solution prepared in step c to provide the ACE-inhibiting composition. Claims 14, 15, 17-19, and 22-27 depend either directly or indirectly from claim 13.

Applicant respectfully submits that the claims are not *prima facie* obvious in view of the cited documents. To establish a *prima facie* case of obviousness, the Examiner has the burden to establish three basic elements. First, the Examiner must establish that there is some suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention. Second, the Examiner must establish that there is a reasonable expectation of success. Finally, the Examiner must establish that the prior art documents teach or suggests all the claim limitations. M.P.E.P. § 2143.

The Examiner rejected claims 1-3, 5, and 7-32 under 35 U.S.C. § 103(a), alleging that those claims are unpatentable over JP 4282398 or JP 04282400 taken with JP 04082898. Applicant respectfully submits that the Examiner has not established that there would have been suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the document or to combine document teachings so as to arrive at the claimed invention. All three of the cited Japanese documents perform extensive purification to provide a purified peptide. In the instant claims, a crude hydrolysate is dried to provide the ACE-inhibition composition. There would have been no suggestion in the cited documents to stop any process to dry a crude hydrolysate in order to prepare an ACE-inhibiting composition.

Applicant also submits that even if there would have been a motivation to combine the cited documents so as to arrive at the claimed process, *arguendo*, the Examiner has not established that the art worker would have had a reasonable expectation of obtaining an ACE-inhibiting composition with any useful activity by drying the hydrolysate. As discussed, all three documents direct the art worker to perform extensive purification to provide a purified peptide

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having ACE-inhibiting properties. It is respectfully submitted that this would have directed the art worker away from stopping the processes at an earlier point because the art worker would have been taught that the useful ACE-inhibiting peptide is a specific peptide, not the hydrolysate. Thus, Applicant respectfully submits that the cited documents would not have provided the art worker with a reasonable expectation that a useful ACE-inhibiting composition could have been obtained without extensive purification of the hydrolysate. Therefore, even if there were motivation to combine the cited documents, the art worker would not have had a reasonable expectation of success for obtaining a useful ACE-inhibiting composition. For this additional reason, the instant claims are not *prima facie* obvious over the cited documents.

Ju et al. (J. Dairy Sci., 78, 2119-2128 (1995); hereinafter Ju et al.)

Ju et al. relates to food products and describes a process for manipulating gelation properties of whey proteins via limited proteolysis. Ju et al. does not teach or suggest a process for preparing an ACE-inhibiting composition. Ju et al. does not even mention ACE. Thus, it is respectfully submitted that the art worker would not have been motivated to combine Ju et al. with the cited Japanese documents.

The Examiner relies on Ju et al. to allege that it is well known to use porcine trypsin in the claimed process. However, since the claimed process is not *prima facie* obvious over the disclosures of the primary documents, as described hereinabove, it is respectfully submitted that the suggestion of porcine trypsin in Ju et al. does not render the claims *prima facie* obvious over the combination of the cited documents.

Conclusion

Applicant respectfully submits that independent claims 1, 12, and 13 are not *prima facie* obvious in view of the cited documents. Because claims 2, 3, 5, 7-11, and 14-32 depend either directly or indirectly from claims 1, 12, and/or 13, those claims are also not *prima facie* obvious in view of the cited documents. The Examiner is therefore respectfully requested to withdraw the rejections of the claims under 35 U.S.C. § 103(a).

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Additionally, as discussed with the Examiner at the interview, Applicant's process produces a high yield of active material. In contrast, following the extensive purification procedures, the processes of the cited documents would provide only a minimal yield of material. Therefore, the claimed process is an improvement over the processes of the cited documents.

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Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is requested. The Examiner is invited to telephone Applicant's attorney (612-371-2110) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.


Respectfully submitted,
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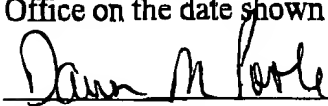
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